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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/981,547
Filing Date: October 17, 2001
Appellant(s): WELLS ET AL.

Ms. Ginger R. Dreger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 2, 2005 appealing from the Office action
mailed May 25, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because claim 58 does not require mass spectrometry

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for (1) detecting the protein-compound conjugate, (2) determining the identity of the non-oligomeric organic compound present in the conjugate and (3) identifying the compound having the greatest relative affinity for the target protein in the library analyzed as purported by Appellants (e.g., see Appeal Brief, page 3, paragraph 1). Claim 58 only requires that the mixture be analyzed by mass spectrometry. Appellants' use of "comprising" terminology does not preclude additional physical methods (e.g., NMR, UV) for accomplishing steps (1)-(3) above. This flaw is also applicable to independent claim 86 and all dependent claims (i.e., all pending claims).

(6) Issues

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

WO 98/11436	Kim et al.	03-1998
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WO 97/01755	Jindal et al.	01-1997
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Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. 1996, pages 119-126

(9) Grounds of Rejection

The following ground of rejection is applicable to the appealed claims:

Claims 58, 59, 61, 65, 81-89, 93, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (WO 98/11436) (Date of Patent is March, 1998) (see IDS, entry

No. 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. 1996, pages 119-126) and Jindal et al. (WO/9701755) (Filing Date is June 26, 1995).

For *claims 58, 86-87*, Kim et al. (see entire document) disclose a method for identifying a ligand that binds to a target protein with the greatest affinity by employing a combinatorial library of non-oligomeric organic compounds using “tethering” techniques (see Kim et al., page 1, paragraph 1; see also page 2, paragraphs 1-2). For example, Kim et al. disclose [a] combining said target protein with a library containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al., see also page 11, paragraph 2, “As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used, potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond”; see also page 17, paragraph 1 disclosing the use of reducing agents, “non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione”). Furthermore, Kim et al. disclose the formation of a target protein-ligand conjugates (e.g., see Kim et al., claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also

page 28, paragraph 1, "This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). Furthermore, Kim et al. disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al., page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection").

In addition, Kim et al. disclose [c-d] the detection of the "most abundant" target protein-compound conjugates and the identification of the non-oligomeric organic compounds present in said conjugates having the "greatest relative affinity" (e.g., see Kim et al., page 17, lines 16-25, "The direct thermodynamic relationship also provides an alternative strategy for identifying ligands from a combinatorial library; molecules that bind with higher affinity will necessarily increase the effective concentration of the other members of the binding pair to a greater extent. Thus, in this embodiment, tethered ligands that bind with higher affinity will have disulfide bonds that are more resistant to reduction by external reducing agents, such as reduced glutathione"; see also Example 1, especially page 26, last paragraph wherein Glutathione is used in different "ratios" to determine the ligand with the highest affinity, "The biotinylated SH3 domain derivatives and the corresponding synthetic linkers (SH3 : linker; 1:10) are incubated with the library of compounds, in Tris buffer (10 mM, pH 7.5), in the presence of a redox system (e.g., reduced glutathione (GSH) and oxidized glutathione (GSSG) at various ratios"). In other words, only the non-oligomeric organic ligands with the "highest affinity" will

remain resistant to the highest “ratios” of reduced/oxidized glutathione. Consequently, the method would also identify the most abundant target protein-compound conjugate because, at least for the highest ratios of reduced/oxidized glutathione, the conjugate formed using the “non-oligomeric organic compound having the greatest relative affinity” would be the only one that exists at the higher ratios of reduced/oxidized glutathione. Finally, Kim et al. disclose “determining the identity” of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al., abstract, “Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands”; see also Summary of the Invention; see also page 8, lines 18-20).

For *claims 59, 61, 88 and 89*, Kim et al. does not explicitly state that the ligands are “less than about 2000 daltons in size” or “less than 1500 daltons “ or “less than 750 daltons” (see claims 58, 59 and 61), but Kim et al. does disclose ligands selected from the group consisting of “small organic molecules, pharmaceuticals, toxins” (see Kim et al., page 21, lines 15-20; see also claim 3 further disclosing “steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin”), which would encompass molecules that are less than 750 daltons in size. “When the PTO shows a sound basis for believing that the products of the Appellant and the prior art are the same, the Appellant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ

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430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For *claims 65 and 93*, Kim et al. does not explicitly state that the target protein is a “TNF receptor” (e.g., see claim 65), but Kim et al. does disclose ligands that are “membrane proteins”, which would encompass proteins like TNF receptors because TNF receptors are “membrane proteins” (e.g., see claims 12, 43). “When the PTO shows a sound basis for believing that the products of the Appellant and the prior art are the same, the Appellant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For *claims 81, 82*, Kim et al. teach obtaining a target protein comprising a –SH group, masked –SH group, or activated –SH group (e.g., see Kim et al., claims 1-2, “target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange”; see also page 3, paragraphs 2-3; see also page 11, line 11 wherein a “cysteine” residue is disclosed).

For *claims 83-85, 95 and 96*, Kim et al. do not explicitly state that the library must comprise “at least 25 members” or “at least 100 members” (see claims 84-85), but Kim et al. do state that libraries are produced using the split and pool synthesis

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techniques taught by Lam (e.g., see Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J., "A new type of synthetic peptide library for identifying ligand-binding activity" *Nature* 1991, 354, 6348, 82-4), which teaches the formation of libraries with greater than 100 members. "When the PTO shows a sound basis for believing that the products of the Appellant and the prior art are the same, the Appellant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Kim et al. differ from the claimed invention as follows:

For *claim 58 and 86*, Kim et al. is deficient in that it does not specifically teach the use of mass spectrometry.

However, the combined references of Siuzdak and Jindal et al. teach the following limitations that are deficient in Kim et al.:

For *claims 58 and 86*, the combined references of Siuzdak (see entire document) and Kim et al. (see entire document) teach the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen interactions including fragmentation techniques like MS² and MS³ (see pages 119-126, especially figures 6.3-6.6 and Table 6.1). In addition, the combined references of Siuzdak and Kim et al. teach that mass spectroscopy may be applied to "combinatorial libraries" of targets and/or ligands for screening purposes (e.g., see Jindal et al., Field of Invention, "This invention

relates to ... rapid analysis of solutions of a large number of mixed molecular species, commonly called "libraries" ... to select ligands having a desired affinity for a target molecule of interest"; see also page 13, lines 2-7; see also figures 1-2, element 44; figures 3-4, element 136; figure 7A-D).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the "affinity enhancing" techniques as taught by Kim et al. with mass spectroscopy as taught by the combined references of Siuzdak and Jindal et al. because Jindal et al., for example, explicitly state that mass spectrometry can be applied to the study of target/ligand interactions including the use of combinatorial libraries (e.g., see Jindal et al., Field of Invention), which would encompass the libraries disclosed by Kim et al. (i.e., the references represent analogous art). In addition, a person of skill in the art would have been motivated to use mass spectroscopy as disclosed by the combined references of Siuzdak and Jindal et al. because Jindal et al., for example, state that their technique improves upon the prior art by increasing the speed by which the target/ligand interactions can be screened, facilitating the use of automation, increasing the sensitivity of the method, and provides enough information about the ligand to facilitate its molecular "identification" thus preventing the need for further characterization by some other analytical technique (e.g., see Jindal et al., page 5, paragraphs 1-2, "Accordingly, the present invention is directed to rapid, efficient and automated ... methods ... for screening libraries to select ... a candidate ligand ... for a preselected target molecule" Additionally, the present invention ... overcomes the disadvantages of the methods known in the art"; see also page 3,

lines 11-24, "Screening methods known in the art thus are not entirely satisfactory ... existing systems are unable selectively to screen a library while simultaneously determining the affinity of selected ligands for the target ... [another] major hurdle [that has been overcome by the present invention] ... is effective chemical characterization of ligands identified in these processes ... A major focus ... is to enable the collection of enough of or enough information about a ligand of interest so as to permit determination of its structure [i.e., using mass spectroscopy]"). Furthermore, Jindal et al. explicitly state that mass spectroscopy is the method of choice for studying libraries (e.g., Jindal et al., page 26, lines 12-15, "The integrated coupling of various dimensions such as ... electrospray ionization mass spectrometry in an automated multi-dimensional system should permit a highly sensitive and highly selective approach to decoding complex mixtures [i.e., mass spectroscopy is the method of choice for libraries]"). Finally, a person of skill in the art would reasonably have been expected to be successful because both Jindal et al. and Kim et al. state that their screening methods are widely applicable to a wide range of target/ligand interactions (e.g., both references disclose the use of small molecule pharmaceuticals, phage libraries, peptide, proteins, antibody/antigen, etc.).

In addition, Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" including antibody-antigen interactions (e.g., see Siuzdak, figures 6.3, 6.5; see especially paragraph bridging pages 125-126, "Electrospray mass spectrometry has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the

“antibody-antigen” complexes disclosed by Kim et al. (e.g., see Kim et al., page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both “covalent” and “non-covalent” interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al. (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has “demonstrated its potential” for these systems (see Siuzdak, page 126, paragraph 1).

In addition, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al. with the “antibody-antigen” complexes as described by Kim et al. because Siuzdak et al. discloses that BOTH “covalent” and “non-covalent” interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak et al., page 123, paragraph 3, “Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al. to work the modified antibodies must bind “covalently” to their respective antigens (see Kim et al., figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody). Therefore, any analytical technique that can confirm the “covalent” attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to “identify” even a “known” ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to

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ascertain whether the modified ligand is truly able to bind to its respective target via a “covalent” bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the “modified” ligands and/or targets as disclosed by Kim et al. with electrospray mass spectroscopy as disclosed by Siuzdak et al. to find modified ligands that can “covalently” bind to the targets as opposed to any unwanted “non-covalent” interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak (just like Jindal et al. and possibly hundreds to thousand of other references that are too numerous to list in this rejection) shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5).

(10) Response to Argument

Argument 1:

Appellants argue, “[i]t is well established that the Office personnel must accept an opinion from a qualified expert based on relevant facts. It is improper to disregard such opinion solely because the Examiner disagrees with its conclusions. This is exactly what happened in the present case. While the Examiner has acknowledged that declarant, and the sold author of the cited Siuzdak reference, is unquestionably an expert in the field, Dr. Siuzdak’s conclusions were dismissed, since they were allegedly contradicted by Jindal et al. and by ‘potentially hundred if not thousands of references,’ none of which were cited or applied against the claims pending ... Indeed, it would be surprising if the Examiner could cite even one reference (let alone hundred

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or thousands of references) that could validly contradict a renown scientist's explanation and conclusions drawn from his own work" (e.g., see Appeal Brief, page 19, paragraph 1).

Response 1:

The Examiner has not "dismissed" the Siuzdak Declaration as purported. The Declaration was fully considered and found to be non-persuasive. The Siuzdak Declaration under 37 CFR § 1.132 filed 2/28/05 is insufficient to overcome the rejection of claim 58, 59, 61, 65, 81-89, 93, 95 and 96 based upon the Jindal et al. 35 U.S.C. § 103(a) rejection as set forth in the last Office action (i.e., the 5/25/05 Non-final rejection) because: (1) The Siuzdak Declaration does not fully address the current rejection. The Siuzdak Declaration was submitted on 2/28/05, which predates the 5/25/05 Jindal et al. rejection and, as a result, is not applicable to the current rejection. (2) Even if, *assuming arguendo*, the declaration could somehow be extrapolated to address the current Jindal et al. rejection, it is not commensurate in scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716). For example, Dr. Siuzdak states, "I respectfully disagree with the Examiner that the cited statement would have motivated a person skilled in the art to identify a novel ligand by the mass spectrometry detection of a covalently bound protein-ligand conjugate in a mixture" (e.g., see Siuzdak Declaration, section 4.). However, as noted in the Summary of Invention, Appellants' claims do not require the use

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of a mass spectrometer for the “identification” of covalently bound protein-ligand conjugates in a mixture as purported. The claims only require that the mixture be “analyzed” with the use of a mass spectrometer. Thus, additional physical methods can be used for the “identification” step.

In addition, Appellants claims do not require the use of an “unknown” library. For example, “determining the identity of the non-oligomeric organic compound” in step (d) of claim 58 could simply be referring to determining the identity of a known compound that binds to the target. That is, the word “identity” could refer to what the compound does (i.e., “identifying” the compound that binds with the greatest relative affinity) rather than what it is (i.e., “identifying” its molecular structure). The Siuzdak declaration never addresses this point and thus cannot overcome the current rejection. Likewise, Appellants arguments fail to set forth any plausible reason why a “known” compound (i.e., known structure) could not be analyzed with a mass spectrometer. The molecular weights of all the compounds in the library would already be known and, as a result, a person of ordinary skill in the art could simply “identify” the compound that interacts with the target by monitoring changes in the spectrum (e.g., see Siuzdak reference, page 123, figure 6.3 wherein a complex was easily identified using this approach). In addition, Appellants claims do not require the use of a “complex” library that might give rise to spectra that are difficult to interpret or samples that have inherently low sensitivity.

Furthermore, even if, *assuming arguendo*, Appellants’ claims were somehow construed to encompass only unknown, complex samples; the claimed invention would still be rendered obvious by the 35 U.S.C. § 103(a) rejection as set forth above. In this scenario, Appellants’ use of “comprising” terminology does not preclude the use of hyphenated technologies like HPLC-MS, as described by Jindal et al. (e.g., see Jindal et al., abstract wherein an “unknown” sample is

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loaded into an HPLC-MS for analysis), which would produce a "pure" sample before its introduction into the mass spectrometer. Again, the Siuzdak declaration does not address this issue and thus cannot overcome the current rejection. That is, the Siuzdak declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Furthermore, even if, *assuming arguendo*, the Siuzdak declaration addressed the full scope of the claims, which it does not, it would be not be persuasive. The declaration sets forth a mere conclusion (i.e., a person of skill in the art would have been motivated to identify a novel ligand using mass spectrometry or would face difficulties as a result of the samples unknown, complex nature) without providing any supporting factual information. If library mixtures were really hard to characterize as purported by Dr. Siuzdak then the Declarant should have had no trouble documenting this assertion with supporting evidence (e.g., a paper showing that it was hard to analyze a library). This has not been done. Furthermore, the Examiner contends that almost all samples represent a library because it is very difficult to purify any one constituent to homogeneity. Thus, even Dr. Siuzdak's own book shows the successful application of a mass spectrometer for the purposes of analyzing a library, albeit a small one (e.g., see Siuzdak, page 125, figure 6.5 showing many peaks for various isotopes, salts and/or ligand complexes in a single spectra wherein all constituents are unambiguously identified).

With regard to the 'potentially hundred if not thousands of references' statement, the Examiner was merely trying to point out that mass spectrometry is a well known technique and that almost every sample run on a mass spectrometer is "impure" (see above) and thus constitutes a library. Since Appellants' claims do not place any limit on the "complexity" of the

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library, any impure sample must qualify as a library. Furthermore, it would be impossible for the Examiner to submit hundreds/thousands of references on this point as requested and, in any event, Jindal et al. and Siuzdak are more than sufficient to support this conclusion. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Argument 2:

Appellants argue, "As it will be shown, Jindal et al. is yet again from another technical field, addressing a materially different problem from the problem addressed by the present invention, and thus does not contradict the conclusions of the Siuzdak Declaration" (e.g., see Appeal Brief, page 10, paragraph 1).

Response 2:

First, the Examiner notes that no supporting statements have been provided. Second, Jindal et al. disclose methods for the rapid analysis of "library" members that might be useful as ligands to a selected biological target molecule (e.g., see Jindal et al., Field of the Invention), which would encompass the "library" members disclosed by Kim et al. for the detection of ligands to target molecules. Thus, Jindal et al. necessarily represents analogous art.

Argument 3:

Appellants argue that Jindal is not applicable because the present invention "... does not involve ... separation steps, and where a complex mixture of target protein-ligand conjugates and optionally ligand candidates is analyzed by mass spectrometry, allowing the determination of the identity of a particular ligand from among the conjugates and ligand candidates preset, which typically have very similar weights" (e.g., see Appeal Brief, page 10 and 11, especially page 11,

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first full paragraph). Appellants further argue, "Since neither Siuzdak and Jindal et al. address the problem addressed by the present invention, and Siuzdak and Jindal et al. each addresses a different and distinct problem, the motivation to combine these references with Kim et al. is an attempt to arrive at the claimed invention does not derive from the nature of the problem to be solved" (e.g., see Appeal Brief, page 11, paragraph 1). Appellants further argue that motivation cannot be derived from the teachings of the cited prior art for essentially the same reasons (e.g., see Appeal Brief, pages 11 and 12, "Dr. Siuzdak ... unambiguously states ... one would not have assumed that a similar approach would work 'to identify novel ligands by mass spectrometry analysis of a mixture of unknown chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected.'"). Finally, Appellants argue that motivation cannot be derived from the knowledge of persons of ordinary skill in the art stating, "The Examiner's attempt to discredit Dr. Siuzdak's statements by citing a reference (Jindal et al.) using mass spectrometry is a method that significantly differs from the method of the present invention is not sufficient to overcome this presumption (e.g., see Appeal Brief, page 12, paragraph 2).

Response 3:

In response to Appellant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

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1992). In this case, a person of skill in the art would have been motivated to use mass spectroscopy as disclosed by the combined references of Siuzdak and Jindal et al. because Jindal et al., for example, state that their technique improves upon the prior art by increasing the speed by which the target/ligand interactions can be screened, facilitating the use of automation, increasing the sensitivity of the method, and provides enough information about the ligand to facilitate its molecular "identification" thus preventing the need for further characterization by some other analytical technique (e.g., see Jindal et al., page 5, paragraphs 1-2, "Accordingly, the present invention is directed to rapid, efficient and automated ... methods ... for screening libraries to select ... a candidate ligand ... for a preselected target molecule" Additionally, the present invention ... overcomes the disadvantages of the methods known in the art"; see also page 3, lines 11-24, "Screening methods known in the art thus are not entirely satisfactory ... existing systems are unable selectively to screen a library while simultaneously determining the affinity of selected ligands for the target ... [another] major hurdle [that has been overcome by the present invention] ... is effective chemical characterization of ligands identified in these processes ... A major focus ... is to enable the collection of enough of or enough information about a ligand of interest so as to permit determination of its structure [i.e., using mass spectroscopy]"). Furthermore, Jindal et al. explicitly state that mass spectroscopy is the method of choice for studying libraries (e.g., Jindal et al., page 26, lines 12-15, "The integrated coupling of various dimensions such as ... electrospray ionization mass spectrometry in an automated multi-dimensional system should permit a highly sensitive and highly selective approach to decoding complex mixtures [i.e., mass spectroscopy is the method of choice for libraries]").

In addition, in response to Appellants argument that the references fail to show certain features of Appellant's invention, it is noted that the features upon which Appellant relies (e.g., a "complex" mixture, "similar molecular weights", "unknown" compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Finally, the Examiner notes "there is no requirement that the prior art provide the same reason as the Appellant to make the claimed invention" (e.g., see MPEP § 2144). Thus, Appellants statement that "neither Siuzdak nor Jindal et al. address the problem addressed by the present invention ... the motivation to combined these references ... does not derive from the nature of the problem to be solved" is not at issue here.

Argument 4:

Appellants argue, "mass spectrometry is nowhere mentioned or suggested [in Kim et al.]" (e.g., see Appeal Brief, page 11, paragraph 2).

Response 4:

In response to appellants' arguments against the Kim et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Argument 5:

Appellants argue that the references, even if they could be properly combined, do not make obvious the claimed invention because, according to Dr. Siuzdak, mass spectrometry is not

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well suited for identifying “unknown” components in a mixture as the spectra difficult to obtain from the tendency of mixtures to reduce the sensitivity of the spectrometer and the spectra are also “difficult or impossible to interpret” from presumably the large number of signals that are produced (e.g., see Appeal Brief, pages 12 and 13).

Response 5:

Again, Appellants arguments are not commensurate in scope with the claims. For example, the claims do not require the use of an “unknown” library. For example, “determining the identity of the non-oligomeric organic compound” in step (d) of claim 58 could simply be referring to determining the identity of a known compound that binds to the target. That is, the word “identity” could refer to what the compound does (i.e., “identifying” the compound that binds with the greatest relative affinity) rather than what it is (i.e., “identifying” its molecular structure). The Siuzdak declaration never addresses this point and thus is not commensurate in scope with the claims. Likewise, Appellants arguments fail to set forth any plausible reason why a “known” compound (i.e., known structure) couldn’t be analyzed with a mass spectrometer. The molecular weights of all the compounds in the library would already be known and, as a result, it would be a simple matter to “identify” the one that interacts with the target by monitoring shifts in the molecular weight (e.g., see Siuzdak reference, page 123, figure 6.3 wherein the complex was easily identified). In addition, Appellants claims do not require the use of a “complex” library that might give rise to spectra that are difficult to interpret or samples that have inherently low sensitivity.

Furthermore, even if, *assuming arguendo*, Appellants’ claims were somehow construed to encompass only unknown, complex samples; the claimed invention would still be rendered

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obvious by the 35 U.S.C. § 103(a) rejection as set forth above. In this scenario, Appellants' use of "comprising" terminology does not preclude the use of hyphenated technologies like HPLC-MS, as described by Jindal et al. (e.g., see Jindal et al., abstract wherein an "unknown" sample is loaded into an HPLC-MS for analysis), which would produce a "pure" sample before its introduction into the mass spectrometer. Again, the Siuzdak declaration does not address this issue and thus cannot overcome the current rejection. That is, the Siuzdak declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Finally, even if, *assuming arguendo*, the Siuzdak declaration addressed the full scope of the claims, which it does not, it would be not be persuasive. The declaration sets forth a mere conclusion (i.e., a person of skill in the art would have been motivated to identify a novel ligand using mass spectrometry or would face difficulties as a result of the samples unknown, complex nature) without providing any supporting factual information. If library mixtures were really hard to characterize as purported by Dr. Siuzdak then the Declarent should have had no trouble documenting this assertion with supporting evidence (e.g., a paper showing that it was hard to analyze a library). This has not been done. Furthermore, the Examiner contends that almost all samples represent a library because it is very difficult to purify any one constituent to homogeneity. Thus, even Dr. Siuzdak's own book shows the successful application of a mass spectrometer for the purposes of analyzing a library, albeit a small one (e.g., see Siuzdak, page 125, figure 6.5 showing many peaks for various isotopes, salts and/or ligand complexes in a single spectra wherein all constituents are unambiguously identified).

Argument 6:

Appellants argue, "Since the cited paragraph has not reference to mass spectrometry detection, and does not state, suggest or imply that mass spectrometry detection would be responsible for or even part of the reasons for the stated advances, it has no bearing on the patentability of the invention claimed in the present application" (e.g., see Appeal Brief, pages 13 and 14, especially page 14, last full paragraph). Appellants also make a similar point with regard to the cited passage on page 26, lines 12-15 (e.g., see Appeal Brief, page 14).

Response 6:

The Examiner respectfully disagrees. The cited passage states, "the present invention is directed to rapid, efficient, and automated ... methods ... for screening libraries to select ... a candidate ligand ... for a pre-selected target molecule" (e.g., see Jindal et al., page 3, lines 11-24). Appellants somehow conclude that since this statement never explicitly uses the words "mass spectrometer" that we cannot assume that a mass spectrometer has anything to do with the currently claimed advantages. This assertion is false. For example, the cited passage refers to "the present invention ...", which is defined in the claims to include a mass spectrometer (e.g., see claim 2, "The method of claim 1 comprising the additional ... inserting the sample into a mass spectrometer to determine the charge-to-mass ratio of said ligand"; see also claim 24, 25, 43, 47 and 48). Furthermore, the abstract, summary of the invention, figures and examples all refer to mass spectrometry as a "preferred" embodiment (e.g., see also abstract; see also figures 3 and 4 element 136, element 136; see also figure 7A-7D show various mass spectra). Thus, an interpretation that the claimed invention has nothing to do with mass spectrometry is simply unreasonable. Furthermore, even if, *assuming arguendo*, some other features were responsible

for the improvement; “there is no requirement that the prior art provide the same reason as the Appellant to make the claimed invention” (see MPEP § 2144).

Argument 7:

Appellants argue, “If possible, statement (2) has even less bearing on the issue of obviousness of the cleaved invention claimed in the present application ... [because] [t]he selectively cited statements are from the “Background” section of the Jindal et al. PCT publication” (e.g., see Appeal Brief, page 14, last paragraph).

Response 7:

The “Background” section is relevant because Jindal et al. indicate that their invention overcomes the disadvantages described in the background of the invention (e.g., see page 5, paragraphs 1 and 2).

Argument 8:

Appellants argue, “The Examiner’s substitution of his own thought in the middle of citations, such as ‘[that has overcome by the present invention]’ and ‘[i.e., using mass spectroscopy]’ is particularly troubling. As noted above, the cited paragraphs are from the Background section of the Jindal et al. PCT publication. While one can assume that these statements are present to emphasize the disadvantages of the prior art methods, and lead up to explaining the advanced represented by the Jindal et al. invention over such prior art methods, there is nothing in the cited statements that would indicate which, if any, of the alleged drawbacks of prior art methods have overcome by Jindal et al., and what part, if any, mass spectrometry has played in the alleged advances represented by the Jindal et al. invention” (e.g., see Appeal Brief, page 15, middle paragraph).

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Response 8:

The Examiner agrees with Appellants that "... one can assume that these statements are present to emphasize the disadvantages of the prior art methods, and lead up to explaining the advance[ments] represented by the Jindal et al. invention over such prior art method."

Furthermore, these assumptions are justified because the Jindal et al. subsequently outlines how their invention, which uses a mass spectrometer, accomplishes the stated goals. For example, Jindal et al. state, "the claimed invention provides a method, system and apparatus [e.g., see claim 44, "The apparatus of claim 43 wherein said means is a mass spectrometer"] for obtaining information about a particular ligand without the need for manual manipulations, regardless of the size of the sample, or the amount of ligand present in the sample. Thus, Jindal et al. confirms that they have overcome the prior art methods that "the need for large amounts of ligands" because as explained by Jindal et al. they can obtain information "regardless off the size of the sample, or the amount of ligand present in the sample" (e.g., see also, "The techniques described in the specification and claims herein provide a multidimensional approach to screening samples, in which separations, chemical reactions, and mass spectrometry are integrated, and, preferably, automated" showing that limitations in automation were overcome; this also confirms statement (1) "the present invention is directed to rapid, efficient and automated ... methods ... for screening libraries"). Thus, the background section does highlight the problems that were overcome in the art and the "mass spectrometer" was a "preferred", "claimed" embodiment for achieving these results. In addition, as mentioned above even if, *assuming arguendo*, some other features were responsible for the improvement; "there is no requirement that the prior art provide the same reason as the Appellant to make the claimed invention" (see MPEP § 2144).

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Argument 9:

Appellants argue, "Turning to citation (3), the full sentence from page 26, lines 12-15 of Jindal et al. ... coupling micro column affinity chromatography with capillary reverse phase HPLC/electrospray ionization mass spectrometry 'should' permit a highly sensitive and selected approach to decoding complex mixtures. There is nothing in the statement that would indicate that electrospray ionization mass spectrometry alone, without being combined with micro column affinity chromatography would provide the stated benefits" (e.g., see Appeal Brief, paragraph bridging pages 15 and 16; see also page 16, first full paragraph).

Response 9:

First, the Examiner notes again that there is no requirement for the mass spectrometer "alone" to provide the stated benefits (e.g., see MPEP § 2144, "there is no requirement that the prior art provide the same reason as the Appellant to make the claimed invention"). Second, even if, *assuming arguendo*, that the mass spectrometer alone had to provide the stated benefits, the Jindal et al. reference provides explicit support for this position. For example, one of the stated benefits is "high sensitivity" (e.g., see Appeal Brief, page 15, second to last line), which undoubtedly refers to the qualities of the detector. Thus, the only question that need be answered is whether the claimed mass spectrometer falls within the scope of a high sensitivity detector. Clearly the answer is yes (e.g., see page 6, last paragraph, "In yet other embodiments, the apparatus comprises ... a detector such as a mass spectrometer"; see also section D, "Detection, "Additional methods of detection include, for example, any apparatus for obtaining mass to-charge ratio, including, but not limited to: matrix-assisted laser desorption ionization/plasma desorption ionization, electrospray ionization, thermospray ionization, and fast atom

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bombardment ionization ... The preferred method of detection and analysis is an improved time of flight instrument which allows independent control of potential on sample and extraction elements"; see also page 40, lines 5-10, "... only a small portion of the flow from the LC eluant stream is injected into the MS analysis stream. The sample volume of the sample loop tubing 32 can be selected to have a negligible effect on the LC stream, yet be sufficient for the MS analysis", which suggests that the MS detection is "highly sensitive" because a lower sensitivity detector would not be able to detect these minute quantities). In addition, a person of ordinary skill in the art would readily recognize that a mass spectrometer is one of the most sensitive analytical instruments known in the art (e.g., see Henry et al., "Fourier-transform mass spectrometry of large molecules by electrospray ionization PNAS 1989, 86, 9075-9078 (of record), page 9078, paragraph 1, "FTMS has the special sensitivity advantage").

Argument 10:

Appellants argue, "Jindal et al. do not disclose mass spectrometry for the analysis of target protein-ligand conjugates ... Jindal et al. ... use ... mass spectrometry ... to detect peptides following various chromatographic ... separation steps" (e.g., see Appeal Brief, page 16, second full paragraph).

Response 10:

In response to Appellant's arguments against the Jindal et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Argument 11:

Appellants argue, "Since Jindal et al. do not teach or suggest the use of mass spectrometry to analyze a mixture comprising target protein-compound conjugates, to detect the most abundant target protein-conjugate this reference does not contradict the conclusion of the Siuzdak Declaration that as person skilled in the art would not have assumed "that mass spectrometry techniques to study enzymatic mechanisms would have been applicable to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture and determining the identity of the ligand present in the conjugate detected" (e.g., see Appeal Brief, paragraph bridging pages 16 and 17).

Response 11:

Again, Appellants arguments are not commensurate in scope with the claims. For example, the claims do not require the use of "unknown" chemical entities. For example, "determining the identity of the non-oligomeric organic compound" in step (d) of claim 58 could simply be referring to determining the identity of a known compound that binds to the target. That is, the word "identity" could refer to what the compound does (i.e., "identifying" the compound that binds with the greatest relative affinity) rather than what it is (i.e., "identifying" its molecular structure). The Siuzdak declaration never addresses this point and thus is not commensurate in scope with the claims. Likewise, Appellants arguments fail to set forth any plausible reason why a "known" compound (i.e., known structure) couldn't be analyzed with a mass spectrometer. The molecular weights of all the compounds in the library would already be known and, as a result, it would be a simple matter to "identify" the one that interacts with the

target by monitoring shifts in the molecular weight (e.g., see Siuzdak reference, page 123, figure 6.3 wherein the complex was easily identified).

Furthermore, even if, *assuming arguendo*, Appellants' claims were somehow construed to encompass only unknown chemical entities; the claimed invention would still be rendered obvious by the 35 U.S.C. § 103(a) rejection as set forth above. In this scenario, Appellants' use of "comprising" terminology does not preclude the use of hyphenated technologies like HPLC-MS, as described by Jindal et al. (e.g., see Jindal et al., abstract wherein an "unknown" sample is loaded into an HPLC-MS for analysis), which would produce a "pure" sample before its introduction into the mass spectrometer. Again, the Siuzdak declaration does not address this issue and thus cannot overcome the current rejection. That is, the Siuzdak declaration does not show that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Finally, even if, *assuming arguendo*, the Siuzdak declaration addressed the full scope of the claims, which it does not, it would be not be persuasive. The declaration sets forth a mere conclusion (i.e., a person of skill in the art would have been motivated to identify a novel ligand using mass spectrometry or would face difficulties as a result of the samples unknown, complex nature) without providing any supporting factual information. If library mixtures were really hard to characterize as purported by Dr. Siuzdak then the Declarent should have had no trouble documenting this assertion with supporting evidence (e.g., a paper showing that it was hard to analyze a library). This has not been done. Furthermore, the Examiner contends that almost all samples represent a library because it is very difficult to purify any one constituent to homogeneity. Thus, even Dr. Siuzdak's own book shows the successful application of a mass

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spectrometer for the purposes of analyzing a library, albeit a small one (e.g., see Siuzdak, page 125, figure 6.5 showing many peaks for various isotopes, salts and/or ligand complexes in a single spectra wherein all constituents are unambiguously identified).

Argument 12:

Appellants argue, "In conclusion, the out of context quotes from Jindal et al., generously supplemented by the Examiner's own thoughts, do not support the rejection, rather are an illustration of the Examiner's attempt of hindsight reconstruction of the claimed invention, based on the Examiner's own notion of common knowledge in the art, and despite an expert's Declaration to the contrary ... the Examiner in fact bases the present rejection on the unsupported and preconceived notion that the use of mass spectrometry for the purpose used in the present application was common knowledge ... This is particularly clear in view of the misinterpretation of Jindal ... Since the Examiner clearly has substituted his own opinion for actual relevant evidence ... the Board should conclude that Examiner has not set forth a prima facie case of obviousness" (e.g., see Appeal Brief page 17).

Response 12:

In response to Appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

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Furthermore, the Examiner notes that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial results include a rapid, efficient, automated method that can determine the affinity of a ligand for a selected target and also the structure of said ligand using a highly sensitive detection system (e.g., see above). Furthermore, this position has been amply supported by the cited passages in the rejection and as outline above in this response.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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